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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,481	01/20/2004	Nozer M. Mehta	P/546-280	2921

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EXAMINER	
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1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/761,481	MEHTA ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15,17-53,55-61 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,17-41,43-53,55-59,61 and 63* is/are rejected.

7)☒ Claim(s) *42 and 60* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20090728*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on July 28, 2009 has been entered.

2. Claims 1-15, 17-36, 43-48, 50-53, 61, and 63 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicant(s) regard as their invention. Evidence that claims fail(s) to correspond in scope with that which applicant(s) regard as the invention can be found in the declaration under 37 CFR 1.132 by Inventor Stern filed July 28, 2009, section 6, and in the Remarks filed July 28, 2009, page 16, lines 1-4. In the declaration and Remarks, Applicants have stated that naturally occurring LHRH is not amidated at its C-terminus, and that LHRH which is amidated at its C-terminus is amidated at a location where the peptide is not naturally amidated. These statements indicate that the invention is different from what is defined in the claim(s), because, e.g., the Schally lecture (Nobel lecture, 08 December 1977) at page 417, Figure 14; Constantinides et al (U.S. Patent Application Publication 2005/0079145) at paragraph [0013]; and Shields (U.S. Patent No. 3,853,834) at column 1, lines 12-19; teach that naturally occurring LHRH is amidated at its C-terminus. While Applicants are entitled to be their own lexicographers, Applicants are not permitted to define terminology contrary to its art-accepted meaning where the written description of the invention has not clearly redefined the terms. See MPEP 2173.05(a)(III). Applicants' specification does not clearly redefine "peptide amidated at a location that is not naturally amidated" or "amidating…

luteinizing hormone-releasing hormone at a location that is not naturally amidated" so as to include LHRH, which is naturally amidated at its C-terminus. Accordingly, it is not clear if the instant claims embrace a peptide which is naturally occurring LHRH and which is naturally amidated at its C-terminus.

3. Claims 1, 41, 42, 59, and 60 are objected to because of the following informalities: At claim 1, line 4, a comma should be inserted after "amidated". At claim 41, line 2; claim 42, line 2; claim 59, line 2; and claim 60, line 2; "NH2" should be re-written as "NH_2". Appropriate correction is required.

4. The effective filing date of instant claims 1-15, 17-53, 55-61, and 63 is January 21, 2003, the filing date of provisional application 60/441,856. Instant claims 1-15, 17-53, 55-61, 61, and 63 are deemed to be entitled under 35 U.S.C. 119(e) to the benefit of the filing date of the provisional application because the provisional application, under the test of 35 U.S.C. 112, first paragraph, discloses the claimed subject matter.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 1-8, 12-15, 17-36, 43-47, 49-51, 61, and 63 are rejected under 35 U.S.C. 102(b) as being anticipated by Stern et al (U.S. Patent No. 6,086,918) as evidenced by the Schally lecture (Nobel lecture, 08 December 1977), Constantinides et al (U.S. Patent Application Publication 2005/0079145), and Shields (U.S. Patent No. 3,853,834). Stern et al teach oral administration of luteinizing hormone-releasing factor using a carrier comprising a pH-lowering agent, an absorption enhancer, a non-physiologically active protein, a gelatin capsule, and an enteric coating. See, e.g., column 6, lines 5-6; column 6, line 63 - column 12, line 10; and claims

1-55. Stern et al are deemed to teach oral administration of luteinizing hormone-releasing factor, because Stern et al explicitly name and exemplify luteinizing hormone-releasing factor, and because the only context in which luteinizing hormone-releasing factor is disclosed by Stern et al is in the context of peptides which can be orally administered using the carriers of Stern et al. See Perricone v. Medicis Pharmaceutical Corp., 432 F3d 1368, 77 USPQ2d 1321, 1326 (Fed. Cir. 2005). Stern et al's "luteinizing hormone-releasing factor" is a synonym for luteinizing hormone-releasing hormone (LHRH). The Schally lecture at page 417, Figure 14; Constantinides et al at paragraph [0013]; and Shields at column 1, lines 12-19; teach that LHRH is amidated at its C-terminus. This rejection assumes that the peptides recited in the rejected claims embrace naturally occurring LHRH, which is amidated at its C-terminus. See also the above rejection under 35 U.S.C. 112, second paragraph. With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. With respect to independent claims 45 and 61, because Stern et al's luteinizing hormone-releasing factor is naturally amidated at its C-terminus, inherently there must have been an amidating step whereby the amidated luteinizing hormone-releasing factor was formed. Note that the claims do not specify any particular amidation process steps.

7. Claims 5 and 48 are rejected under 35 U.S.C. 103(a) as being obvious over Stern et al (U.S. Patent No. 6,086,918) as evidenced by the Schally lecture (Nobel lecture, 08 December 1977), Constantinides et al (U.S. Patent Application Publication 2005/0079145), and Shields (U.S. Patent No. 3,853,834) as applied against claims 1-8, 12-15, 17-36, 43-47, 49-51, 61, and 63 above, and further in view of Stern et al (U.S. Patent No. 5,912,014). Stern et al teach

luteinizing hormone-releasing factor, which is amidated at its C-terminus, but does not teach synthesizing this peptide by forming a glycine-extended precursor and then converting the glycine residue to a C-terminal amide group. Stern et al '014 teaches salmon calcitonin made with a C-terminal glycine extension which is enzymatically converted to an amide group. See, e.g., column 5, lines 12-23. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the luteinizing hormone-releasing factor of Stern et al by synthesizing the peptide as a glycine-extended precursor and then converting the glycine residue to a C-terminal amide group, because Stern et al '014 teach that this is a known reaction technique for forming a C-terminally amidated peptide, and because the particular method of synthesizing a peptide would not have been expected to affect the in vivo activity of the peptide.

8. Claims 1-15, 17-36, 43-47, 49-53, 61, and 63 are rejected under 35 U.S.C. 102(a) as being anticipated by the WO Patent Application 02/043767 as evidenced by the Schally lecture (Nobel lecture, 08 December 1977), Constantinides et al (U.S. Patent Application Publication 2005/0079145), and Shields (U.S. Patent No. 3,853,834). The WO Patent Application '767 teaches oral administration of luteinizing hormone-releasing factor linked to a membrane translocator using a carrier comprising a pH-lowering agent, a protease inhibitor, an absorption enhancer, a non-physiologically active peptide, a gelatin capsule, and an enteric coating. See, e.g., page 17, line 18; page 18, lines 10-27; page 20, lines 11-29; and claims 1-57. [Note that the WO Patent Application '767 does not designate the US, and therefore is not available as prior art under 35 U.S.C. 102(e).] The WO Patent Application '767 is deemed to teach oral administration of luteinizing hormone-releasing factor, because the WO Patent Application '767 explicitly names and exemplifies luteinizing hormone-releasing factor, and because the only

context in which luteinizing hormone-releasing factor is disclosed by the WO Patent Application '767 is in the context of peptides which can be orally administered using the carriers of the WO Patent Application '767. See Perricone v. Medicis Pharmaceutical Corp., 432 F3d 1368, 77 USPQ2d 1321, 1326 (Fed. Cir. 2005). The WO Patent Application '767's "luteinizing hormone-releasing factor" is a synonym for luteinizing hormone-releasing hormone (LHRH). The Schally lecture at page 417, Figure 14; Constantinides et al at paragraph [0013]; and Shields at column 1, lines 12-19; teach that LHRH is amidated at its C-terminus. This rejection assumes that the peptides recited in the rejected claims embrace naturally occurring LHRH, which is amidated at its C-terminus. See also the above rejection under 35 U.S.C. 112, second paragraph. With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. With respect to independent claims 45 and 61, because the WO Patent Application '767's luteinizing hormone-releasing factor is naturally amidated at its C-terminus, inherently there must have been an amidating step whereby the amidated luteinizing hormone-releasing factor was formed. Note that the claims do not specify any particular amidation process steps.

9. Claims 5 and 48 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 02/043767 as evidenced by the Schally lecture (Nobel lecture, 08 December 1977), Constantinides et al (U.S. Patent Application Publication 2005/0079145), and Shields (U.S. Patent No. 3,853,834) as applied against claims 1-15, 17-36, 43-47, 49-53, 61, and 63 above, and further in view of Stern et al (U.S. Patent No. 5,912,014). The WO Patent Application '767 teaches luteinizing hormone-releasing factor, which is amidated at its C-terminus, but does not teach synthesizing this peptide by forming a glycine-extended precursor

and then converting the glycine residue to a C-terminal amide group. Stern et al '014 teaches salmon calcitonin made with a C-terminal glycine extension which is enzymatically converted to an amide group. See, e.g., column 5, lines 12-23. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the luteinizing hormone-releasing factor of the WO Patent Application '767 by synthesizing the peptide as a glycine-extended precursor and then converting the glycine residue to a C-terminal amide group, because Stern et al '014 teach that this is a known reaction technique for forming a C-terminally amidated peptide, and because the particular method of synthesizing a peptide would not have been expected to affect the in vivo activity of the peptide.

10. Claims 1-8, 12-15, 17-41, 43-47, 49-51, 55-59, and 63 are rejected under 35 U.S.C. 103(a) as being obvious over Stern et al (U.S. Patent No. 6,086,918) in view of Habener (U.S. Patent No. 5,120,712), Balschmidt et al (U.S. Patent No. 5,157,021), Barbier et al (U.S. Patent No. 6,110,892), the European Patent Application 878,201, or Neiss et al (U.S. Patent No. 4,804,742). Stern et al teach oral administration of peptides such as insulin, salmon calcitonin, parathyroid hormone, and lhrf using a carrier comprising a pH-lowering agent, an absorption enhancer, a non-physiologically active protein, a gelatin capsule, and an enteric coating. See, e.g., column 6, line 1 - column 12, line 10, and claims 1-55. Stern et al do not teach peptides which are amidated GLP-1 analogs, amidated insulin analogs, or amidated PTH analogs. Habener teaches GLP-1 analogs which are amidated. See, e.g., claims 1 and 4. Balschmidt et al teach insulin in which the carboxylic acid groups present in the sidechains at residues A4, A17, B13, and B21 are amidated in order to achieve a long-lasting protracted acting insulin analog. See, e.g., column 2, lines 5-8 and 49-53. Barbier et al teach the human parathyroid hormone

derivatives hPTH(1-34)-OH and hPTH(1-31)NH_2, and teach that the derivatives can be administered orally. See, e.g., column 2, lines 26-44, and column 14, lines 59-62. The European Patent Application '201 teaches the human parathyroid hormone derivative hPTH(1-34)NH_2. See, e.g., column 3, lines 31-36. Neiss et al teach salmon calcitonin amidated at locations which are not naturally amidated and which have extended duration of activity. See, e.g., column 1, lines 42-44, and claims 1 and 2. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the specific peptides of Habener, Balschmidt et al, Barbier et al, the European Patent Application '201, or Neiss et al in the oral administration compositions of Stern et al because the oral administration compositions of Stern et al have general applicability to any peptide and because it would be desirable to be able to administer orally the peptides of Habener, Balschmidt et al, Barbier, the European Patent Application '201, and Neiss et al because oral administration is easier for the patient. Applicants' claims would have been prima facie obvious at the time the invention was made because applying Stern et al's known and generally applicable technique, i.e. of combining peptides with a pH-lowering agent, an absorption enhancer, a non-physiologically active protein, a gelatin capsule, and an enteric coating so that the peptides can be administered orally, to the known and specific peptides of Habener, Balschmidt et al, Barbier et al, the European Patent Application '201, or Neiss et al, with only the expected result that the known and specific peptides of Habener, Balschmidt et al, Barbier et al, the European Patent Application '201, or Neiss et al can be administered orally, is prima facie obvious. See KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (S. Ct. 2007). With respect to instant claim 5, process limitations do not impart novelty and

unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

11. Claims 5 and 48 are rejected under 35 U.S.C. 103(a) as being obvious over Stern et al (U.S. Patent No. 6,086,918) in view of Habener (U.S. Patent No. 5,120,712), Barbier et al (U.S. Patent No. 6,110,892), the European Patent Application 878,201, or Neiss et al (U.S. Patent No. 4,804,742) as applied against claims 1-8, 12-15, 17-41, 43-47, 49-51, 55-59, and 63 above, and further in view of Stern et al (U.S. Patent No. 5,912,014). Habener, Barbier et al, the European Patent Application '201, and Neiss et al teach known and specific peptides which are amidated at their C-termini, but do not teach synthesizing these peptides by forming glycine-extended precursors and then converting the glycine residue to a C-terminal amide group. Stern et al '014 teaches salmon calcitonin made with a C-terminal glycine extension which is enzymatically converted to an amide group. See, e.g., column 5, lines 12-23. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the known and specific peptides of Habener, Barbier et al, the European Patent Application '201, or Neiss et al for use in the oral administration compositions of Stern et al '918 by synthesizing the peptides as glycine-extended precursors and then converting the glycine residue to a C-terminal amide group, because Stern et al '014 teach that this is a known reaction technique for forming a C-terminally amidated peptide, and because the particular method of synthesizing a peptide would not have been expected to affect the in vivo activity of the peptide.

12. Claims 1-15, 17-41, 43-47, 49-53, 55-59, and 63 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 02/043767 in view of Habener (U.S. Patent No. 5,120,712), Balschmidt et al (U.S. Patent No. 5,157,021), Barbier et al (U.S. Patent No.

6,110,892), the European Patent Application 878,201, or Neiss et al (U.S. Patent No. 4,804,742). The WO Patent Application '767 teaches oral administration of peptides such as insulin, salmon calcitonin, parathyroid hormone, lhrf, and GLP-1 linked to a membrane translocator using a carrier comprising a pH-lowering agent, a protease inhibitor, an absorption enhancer, a non-physiologically active peptide, a gelatin capsule, and an enteric coating. See, e.g., page 17, lines 13-22, page 18, lines 10-27, page 20, lines 11-29, and claims 1-57. [Note that the WO Patent Application '767 does not designate the US, and therefore is not available as prior art under 35 U.S.C. 102(e).] The WO Patent Application '767 does not teach peptides which are amidated GLP-1 analogs, amidated insulin analogs, or amidated PTH analogs. Habener teaches GLP-1 analogs which are amidated. See, e.g., claims 1 and 4. Balschmidt et al teach insulin in which the carboxylic acid groups present in the sidechains at residues A4, A17, B13, and B21 are amidated in order to achieve a long-lasting protracted acting insulin analog. See, e.g., column 2, lines 5-8 and 49-53. Barbier et al teach the human parathyroid hormone derivatives hPTH(1-34)-OH and hPTH(1-31)NH_2, and teach that the derivatives can be administered orally. See, e.g., column 2, lines 26-44, and column 14, lines 59-62. The European Patent Application '201 teaches the human parathyroid hormone derivative hPTH(1-34)NH_2. See, e.g., column 3, lines 31-36. Neiss et al teach salmon calcitonin amidated at locations which are not naturally amidated and which have extended duration of activity. See, e.g., column 1, lines 42-44, and claims 1 and 2. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the specific peptides of Habener, Balschmidt et al, Barbier et al, the European Patent Application '201, or Neiss et al in the oral administration compositions of the WO Patent Application '767 because the oral administration compositions

have general applicability to any peptide and because it would be desirable to be able to administer orally the peptides of Habener, Balschmidt et al, Barbier et al, the European Patent Application '201, and Neiss et al because oral administration is easier for the patient. Applicants' claims would have been prima facie obvious at the time the invention was made because applying the WO Patent Application '767's known and generally applicable technique, i.e. of combining peptides with a pH-lowering agent, a protease inhibitor, an absorption enhancer, a non-physiologically active peptide, a gelatin capsule, and an enteric coating so that the peptides can be administered orally, to the known and specific peptides of Habener, Balschmidt et al, Barbier et al, the European Patent Application '201, or Neiss et al, with only the expected result that the known and specific peptides of Habener, Balschmidt et al, Barbier et al, the European Patent Application '201, or Neiss et al can be administered orally, is prima facie obvious. See KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (S. Ct. 2007). With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

13. Claims 5 and 48 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 02/043767 in view of Habener (U.S. Patent No. 5,120,712), Barbier et al (U.S. Patent No. 6,110,892), the European Patent Application 878,201, or Neiss et al (U.S. Patent No. 4,804,742) as applied against claims 1-15, 17-41, 43-47, 49-53, 55-59, and 63 above, and further in view of Stern et al (U.S. Patent No. 5,912,014). Habener, Barbier et al, the European Patent Application '201, and Neiss et al teach known and specific peptides which are amidated at their C-termini, but do not teach synthesizing these peptides by forming glycine-

extended precursors and then converting the glycine residue to a C-terminal amide group. Stern et al '014 teaches salmon calcitonin made with a C-terminal glycine extension which is enzymatically converted to an amide group. See, e.g., column 5, lines 12-23. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to form the known and specific peptides of Habener, Barbier et al, the European Patent Application '201, and Neiss et al for use in the oral administration compositions of the WO Patent Application '767 by synthesizing the peptides as glycine-extended precursors and then converting the glycine residue to a C-terminal amide group, because Stern et al '014 teaches that this is a known reaction technique for forming a C-terminally amidated peptide, and because the particular method of synthesizing a peptide would not have been expected to affect the in vivo activity of the peptide.

14. Claims 1, 4, 5, 17-19, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by the Neugebauer et al article (Biochemistry, Vol. 34, pages 8835-8842). The Neugebauer et al article teaches a composition comprising hPTH(1-31)NH_2 combined with palmitoyloleoyl-phosphatidylserine vesicles in phosphate-buffered solution. See, e.g., page 8836, column 1, second full paragraph, and column 2, second paragraph; page 8839, Figure 7 and paragraph bridging columns 1 and 2. Note that an intended use limitation, e.g., "orally delivered", does not impart patentability to product claims where the product is otherwise anticipated by the prior art. Because the Neugebauer et al article teaches the only components specified in Applicants' claims, i.e. hPTH(1-31) amidated at its C-terminus and a phospholipid, inherently the composition of the Neugebauer et al article will provide enhanced bioavailability of the amidated peptide when it is orally delivered to the same extent claimed by Applicants. Sufficient evidence

of similarity is deemed to be present between the compositions of the Neugebauer et al article and Applicants' claimed compositions to shift the burden to Applicants to provide evidence that the claimed compositions are unobviously different than those of the Neugebauer et al article. With respect to instant claim 5, process limitations do not impart novelty and unobviousness to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

15. Applicant's arguments filed July 28, 2009 have been fully considered but they are not persuasive.

Statements in both the declaration under 37 CFR 1.132 by Inventor Stern filed July 28, 2009, section 6, and in the Remarks at page 16, lines 1-4, indicate that there is a significant lack of agreement between Applicants and the examiner as to the scope of the instant claims, and in particular as to whether the instant claims embrace a peptide which is LHRH amidated at its C-terminus. As indicated in the above rejection under 35 U.S.C. 112, second paragraph, the prior art establishes that naturally occurring LHRH is amidated at its C-terminus. Accordingly, to the extent that Declarant and Applicants argue that LHRH amidated at its C-terminus is representative of the peptides embraced by the instant claims, these arguments contradict the plain and established meaning of the current claim terminology. In response to this Office action, Applicants must: (1) explicitly and clearly state whether they intend for the claimed peptides to embrace naturally occurring LHRH, i.e. LHRH which is amidated at its C-terminus; and (2) if they do so intend, explain how the claim language can be interpreted and/or how the specification and claims can be amended so that it is clear that the claimed peptides embrace naturally occurring LHRH, i.e. LHRH which is amidated at its C-terminus. Assuming,

arguendo, that Applicants intend for the claimed peptides to embrace naturally occurring LHRH, i.e. LHRH which is amidated at its C-terminus, this Office action includes prior art rejections (see sections 6-9 above) specifically directed to such an embodiment, i.e. to oral pharmaceutical compositions wherein the peptide is naturally occurring LHRH, and methods of administering the same.

With respect to the prior art rejections set forth in sections 6-9 above, as noted above, these rejections assume, arguendo, that the claims embrace a peptide which is naturally occurring LHRH, which is amidated at its C-terminus. To the extent that the claims embrace such a peptide, oral administration of such a peptide is taught by Stern et al (U.S. Patent No. 6,086,918) and by the WO Patent Application 02/43767. Evidence of unexpected results can not be relied upon to overcome anticipatory prior art rejections. Alternatively, as noted in the Office action mailed July 30, 2008, page 11, lines 9-12, to the extent that the claims do not embrace a peptide which is naturally occurring LHRH, any showing of unexpected results for such a peptide (in comparison to a non-amidated version of LHRH) would lack any nexus with the claimed invention, and therefore could not be relied upon to rebut any prima facie case of obviousness.

The declaration under 37 CFR 1.132 by Inventor Stern filed July 28, 2009 (Stern II) has been carefully considered but is not deemed to overcome the rejections under 35 U.S.C. 103(a) set forth in this Office action. The Stern II declaration does not provide any additional experimental results supporting Applicants' allegation of unexpected results for the oral administration of amidated peptides, but does provide additional explanations as to why Examples 1, 3, and 4 support the allegation of unexpected results.

With respect to Example 1, the Stern II declaration states that the example clearly establishes that amidation of a peptide improves its bioavailability, i.e. in comparison to bioavailabilities of the corresponding peptide without such amidation. However, as noted in the previous Office action, the example does not set forth a comparison with "the corresponding peptide without such amidation". Rather, the example compares an amidated peptide with a glycine-extended peptide. Declarant's statement is not supported by the comparative testing actually carried out; and Declarant's assertion that "the significant difference between sCT and sCR-gly is not 1 amino acid but the presence of a terminal amide group on sCT" is also not supported by experimental evidence. Further, Stern et al (U.S. Patent No. 6,086,918) and the WO Patent Application 02/0043767 teach salmon calcitonin as a peptide which can be administered orally using their disclosed carriers. In order to rebut a prima facie case of obviousness, an affidavit or declaration under 37 CFR 1.132 must compare the claimed invention with the closest prior art of record, i.e. with the salmon calcitonin taught by Stern et al and the WO Patent Application '767 rather than with glycine-extended salmon calcitonin. See MPEP 716.02(e). Declarant also cites to the Liebisch et al article (PNAS, Vol. 83, pages 1936-1940) as showing that amidation of a peptide at the C-terminus confers carboxypeptidase Y resistance. However, to the extent that the amidated peptides recited in Applicants' claims are resistant to carboxypeptidase Y, such a result is expected, rather than unexpected, in view of the Liebisch et al article, and expected results constitute evidence of obviousness just as unexpected results constitute evidence of nonobviousness. See MPEP 716.02(c)(II).

With respect to Example 3, the Stern II declaration states that intraduodenal administration of peptides is used to model absorption of peptides from an acid resistant

protective vehicle as is described in claim 3, and that such a vehicle is designed to release its contents in the intestine. Both Stern et al (U.S. Patent No. 6,086,918) and the WO Patent Application 02/0043767 require carriers including acid resistant protective vehicles such that their peptides are released in the intestine. Accordingly, Example 3 of the specification is deemed to set forth a showing of unexpected results with respect to oral administration of human parathyroid hormone analog PTH 1-34NH_2. Claims 42 and 60 are therefore no longer rejected under 35 U.S.C. 103(a) based upon stern et al or the WO Patent Application '767 as the primary references.

With respect to Example 4, as noted above, claims 1-15, 17-36, 43-47, 49-53, 61, and 63 may or may not embrace peptide including naturally-occurring LHRH, which is amidated at its C-terminus. To the extent that the claims embrace such a peptide, the claims are anticipated by Stern et al (U.S. Patent No. 6,086,918) and by the WO Patent Application 02/43767. Anticipation cannot be overcome by evidence of unexpected results. In re Malagari , 499 F.2d 1289, 182 USPQ 549, 553 (CCPA 1974). To the extent that the claims do not embrace such a peptide, then the comparative testing of Example 4 is not relevant to the invention as claimed. There is no nexus between unexpected results for an unclaimed peptide and the invention as currently claimed.

As noted above, Applicants are deemed to have demonstrated unexpected results for a single peptide species, human parathyroid hormone analog PTH 1-34NH_2. However, a single comparative result is not deemed to be commensurate in scope with claims not limited to human parathyroid hormone analog PTH 1-34NH_2. In view of the vast number of physiologically active peptide agents, many of which comprise plural non-natural amidation sites, testing of a single

species is not considered to be predictive of unexpected results for the entire genus of claimed peptides.

16. Claims 42 and 60 would be allowable if rewritten to overcome the claim objections set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:00 A.M. to 5:30 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (571) 272-0562. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey E. Russel/
Primary Examiner, Art Unit 1654

JRussel
September 18, 2009